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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,037	02/09/2004	Paul G. Yock	13854.4004	1520

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,037	YOCK ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/9/07 has been entered.

Claims 1-104 are pending in this application.

This application is a reissue if United States Patent Number 6,346,098.

Oath/Declaration

The oath is objected to as.

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76. Specifically, the mailing address of Peter Fitzgerald is missing.

Claim Objections

Claim 3 is objected to because of the following informalities: claim 3 recites "at a site at least proximal to said interstitial space". However, inclusion of "at least" is not necessary as it is not clear what site is more then proximal to the interstitial space. It would be remedial to delete "at least". Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-104 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation that either the agent or a fluid delivery vehicle produces a disruption in the vessel has been added to the claims. Applicant has not indicated where support for this limitation is found. The examiner has been unable to find literal support in the originally filed specification for this limitation. The specification does not teach that either the agent or the fluid delivery vehicle is responsible for causing the disruption of the vessel. Rather, the specification teaches that the agent is "administered in combination with the application of stress to the vascular tissue associated with the vascular site of administration and it is the production of stress that results in disruption of the vascular vessel (see col 4, line 36-46). As well, this stress can be physical, chemical or a combination of the two. By physical is meant mechanical stress such as external forces i.e. electroporation, RF energy. By chemical stress is meant inflammatory agents or tissue disrupting agent. These teachings do not suggest or disclose that the biological agent that is delivered to the vascular vessel is responsible for the disruption. While, the specification teaches that chemical agents can be used to disrupt the vessel, there is no teaching

that the chemical agent is also the biological agent. Therefore, the limitation is impermissible NEW MATTER

Response to Argument

Applicants' arguments filed 3/20/06 have been fully considered but they are not persuasive. Applicants point to the specification at col 5 that teaches, "the flowable formulation of the active agent is introduced into the vascular deposition space in a manner such that mechanical stress" produces a passageway. Thus, the passageways are created by mechanical stress resulting of the flowable formulation. However, the claims are currently drawn to agents and fluids that can cause any number of types of stresses such as chemical stress i.e. the situation in which the agent or fluid alone can cause a passageway such as by means other then mechanical induction of a passageway by both components together. In other words, the claims encompass a variety of conditions that are not supported by the specification. Therefore, the limitation is impermissible NEW MATTER.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7-11, 13-19, 21-23, 29-39, 43-47 and 49-100 stand rejected under 35 U.S.C. 102(e) as being anticipated by Wolff et al (US 6,867,196; see entire document).

Wolff et al teach methods of delivering nucleic acid to cardiac tissue using a catheter (forming a channel) into cardiac tissue from a vessel (vein or artery, see e.g. col 8, line 10-19), The instant specification defines interstitial space as the region or tissue beyond the wall of the vascular site or beyond the intimal space (see e.g. bridging paragraph col 3-4). The method involves a retrograde approach with increased permeability of the vessels as recited in claims 1, 2, 8, 10, 13, 14, 21-23, 30 and 36-38 (see e.g. abstract, col 9, line 4-27 and col 11, line 1-65). Permeability of the vessel is increased by intravascular hydrostatic pressure by the fluid delivery vehicle as recited in claims 15-18, 44, 46, 49-53 (see e.g. col 11, line 1-55), this increased permeability results in channels to the heart and is equal to a disruption in the vessel such that agent is delivered to the interstitial space. Stress is placed proximal to the interstitial space and can be chemical (see e.g. col 11, line 34-54) as recited in claims 3, 29 and 39. As well, the stress can also be mechanical as it is generated by clamping (see e.g. col 11, line 1-21) as recited in claims 7, 9, 43, 45, 56-59, 61, 68, 78-82 and 84. A catheter is used that has an occlusion device downstream of the site of administration of the agent (see e.g. figure 3) as recited in claims 32, 34, 63, 65, 74, 76, 86, 88, 97 and 99. As demonstrated in figure 3 and figure 4, the catheter comprises an occlusion device that is upstream and downstream of the site of administration. The specification does not define venous (venous) branches. During prosecution, claims must be interpreted as broadly as their terms reasonably allow. Thus, as depicted in figure 4, the catheter would place an occlusion device such that at least one upstream branch of the vessel can be occluded as recited in claims 33, 64, 75, 87 and 98. This should necessarily result in disruption

through increased permeability of the venous branches upstream of the vessel as recited in claims 31, 35, 62, 66, 73, 77, 85, 89, 96 and 100. Finally, Wolff et al teach that nucleic acids encoding cytokines can be delivered. Many cytokines are responsible for producing inflammatory responses. Thus it would be inherent that administration of cytokines would lead to production of inflammation in the vessels as recited in claims 11, 19, 47, 55, 60, 71, 83 and 94.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-6, 8, 12, 15, 20, 24, 28, 37, 40-42, 44, 48, 51, 56-59, 61-70, 71-82, 84-93 and 95-104 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (US 6,867,196; see entire document) in view of Makower et al (US 2002/0179098; see entire document).

Applicants claim a method of locally administering an active agent comprising retroinfusing an agent into a vascular vessel under conditions sufficient for an agent or fluid delivery vehicle to produce a disruption which method further comprises administration of energy to the vessel. As well, the agent is delivered to a myocardial space and the agent can be cells or dye or imaging agents, the vessel can be a venous branch.

The teachings of Wolff et al are described above and are applied as before except;

Wolff et al do not teach that the method further comprises administration of energy to the vessel, the agent is delivered to a myocardial space and the agent can be cells or dye or imaging agents.

Makower et al teach a method of locally administering an active agent such as xenograft tissue (which inherently comprise cells, peptides, proteins and nucleic acids) signal emitting targets or radiological imaging material, imaging means or dyes (see e.g. paragraph 0012, 0097, 0109 and 0161) in which the agent is retroinfused into a vascular vessel such as a vein under conditions sufficient to disrupt the vein such that the agent enters interstitial space such as the myocardial space as recited in claims 6, 12, 20, 24, 42 and 48 (see e.g. paragraph 0097). The method further comprises administration of energy to the vein such as heat as recited in claim 5, 28, 41, 56-59, 61-70, 71-82, 84-93 and 95-104 (see e.g. paragraph 0114, claims 75 and 76). Heat is used to keep the non-stented passageways open and to prevent scarring as well as a depot means carrying the cells as recited in claim 4 and 40 (see e.g. paragraph 0169).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to locally deliver to the myocardial beds an agent by retroinfusion such that a disruption results in the vascular vessel to the interstitial space as taught by Wolffe et al in which the disruption is produced in the myocardial interstitial space and to then apply energy such as heat in the method as taught by Makower et al because Wolffe et al teach that it is within the ordinary skill of the art to retroinfuse agents into a vascular vessel such that a passageway to the interstitial space is created and because Makower et al teach that it is within the ordinary skill of the art to deliver agents to the myocardial space following retroinfusion and to apply energy such as heat during the method. One would have been motivated to do so in order to receive the

expected benefit of delivery to the myocardial space to treat coronary artery disease and for revascularization in which a passageway to the myocardial interstitial space has been generated using xenograft tissue and has been treated with heat to decrease incidence of scarring and incidence of closure. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1 and 25-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (US 6,867,196; see entire document).

Applicants claim a method of locally administering an active agent to a host by retroinfusing said agent into the vessel under pressure of at least 50mm Hg, 60 mm Hg and 1000 mm Hg.

The teachings of Wolff et al are described above and are applied as before except;

Wolff et al do not teach that the pressure used during retroinfusion is at least 50mm Hg, 60mm Hg and 1000mm Hg.

It would have been obvious to someone of skill in the art to utilize pressure of at least 50mm Hg, 60 mm Hg and 1000 mm Hg in the method of Wolff et al given that the identification of these pressures would be required to optimize the hydrostatic pressure to permeabilize or disrupt the vessels for deliverance of the agents. A person of skill in the art would have been motivated to optimize these conditions to best utilize the methods of Wolff et al for deliverance of agents to interstitial spaces. The MPEP teaches "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art

unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages"). Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 and 103 on pages 24-27 of the amendment filed 10/9/07. Applicants' arguments filed 10/9/07 have been fully considered but they are not persuasive. On page 25 of the amendment, applicants argue that Wolff only teaches enhanced delivery through natural channels whereas the instant specification utilizes created passageways that are created by disruption of the integrity of the vessel walls.

Wolffe et al teach increasing the intravascular pressure of the blood vessel by increasing osmotic pressure with in the blood vessel with hypertonic solutions or use of chemicals or with "biologically active molecules that affect permeability interact with a specific receptor or enzyme or protein with the vascular cell to change the vessel's permeability". As well Wolffe et al teach, "Permeability" is defined herein as the propensity for macromolecules such as nucleic acids to move through vessel walls and enter the extravascular space. One measure of

permeability is the rate at which macromolecules move through the vessel wall and out of the vessel. Another measure of permeability is the lack of force that resists the movement through the vessel wall and out of the vessel. Vessels contain elements that prevent macromolecules from leaving the intravascular space (internal cavity of the vessel). These elements include endothelial cells and connective material (e.g., collagen). High permeability indicates that there are fewer of these elements that can block the egress of macromolecules and that the spaces between these elements are larger and more numerous. In this context, high permeability enables a high percentage of nucleic acids being delivered to leave the intravascular space, while low permeability indicates that a low percentage of the nucleic acids will leave the intravascular space." In the broadest interpretation, permeability creates disruptions in the wall that are not normally there. The claims are not limited to "disruptive channels" but to disruptions in the vessels and these are encompassed by the teachings of Wolffe et al. Nor is tissue damage a prerequisite for disruption of the vessels. Rather, the condition of enhanced permeability and condition of enhanced larger pores is not a normal state of the vessel, the presence of these large pores signifies a disruption in their normal condition.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633